EXHIBIT A

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

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Addressee
Central File + orig.
S. Dombey
Sr. Staff - circ.
Therapeutic Dir. (I. Martin)

NDA 20-235

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Parke-Davis Pharmaceutical Research
Division of Warner-Lambert Company
Attention: Janeth L. Turner
Worldwide Regulatory Affairs
2800 Plymouth Road
Ann Arbor, Michigan 48105

Date Rec'd JAN 0 5 1994
original -- CBI
D: R.A. V.P.
Therapeutic Dir
IND Coord.

Dear Ms. Turner:

Reference is made to your new drug application dated January 15, 1992 submitted under section 505(b) of the Federal Food, Drug and Cosmetic Act for Neurontin® (Gabapentin) 100, 300, and 400 mg capsules.

We also refer to an Agency Approvable letter dated December 21, 1993 and to your amendments dated:

09/15/92	10/15/92	10/28/92	11/16/92	12/01/92	10/14/93
12/09/93	12/17/93	2/21/93	12/22/93	12/23/93	

We have completed the review of this application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended with the labeling changes noted in the enclosed final draft of labeling that accompanies this letter (as Attachment 1). Accordingly, the application, with these labeling revisions, is APPROVED, effective as of the date of this letter.

We note that in your response of December 23, 1993 you committed to continue your efforts to identify the mechanism of the animal carcinogenic response.

Methods Validation

The validation of the analytical methods has not been completed. We will expect your full cooperation in resolving any problems that may arise.

Labeling/PPI

The final printed labeling (FPL) must be identical to the draft labeling/PPI enclosed as Attachment 1 with this letter. Marketing the product with FPL that is not identical to the draft labeling may render the product misbranded and an unapproved new drug.

Please submit 12 copies of the FPL as soon as it is available. Seven of the copies should be individually mounted on heavy-weight paper or similar material. The submission should be designated for administrative purposes as "FPL for approved NDA 20-235". Approval of the submission by FDA is not required before the labeling may be used. Should additional information relating to the safety and effectiveness of this drug product become available, further revision of the labeling may be required.

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA as set forth under 21 CFR 314.80 and 314.81.

Sincerely yours,

Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

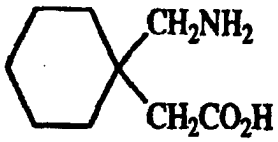
Attachment

December 30, 1993

DESCRIPTION

Neurontin® (gabapentin capsules) is supplied as imprinted hard shell capsules containing 100 mg, 300 mg, and 400 mg of gabapentin. The inactive ingredients are lactose, corn starch, and talc. The 100-mg capsule shell contains gelatin and titanium dioxide. The 300-mg capsule shell contains gelatin, titanium dioxide, and yellow iron oxide. The 400-mg capsule shell contains gelatin, red iron oxide, titanium dioxide, and yellow iron oxide. The imprinting ink contains FD&C Blue No. 2 and titanium dioxide.

Gabapentin is described as 1-(aminomethyl) cyclohexaneacetic acid with an empirical formula of $C_9H_{17}NO_2$ and a molecular weight of 171.24. The molecular structure of gabapentin is:



Gabapentin is a white to off-white crystalline solid. It is freely soluble in water and both basic and acidic aqueous solutions.

CLINICAL PHARMACOLOGY

Mechanism of Action:

The mechanism by which gabapentin exerts its anticonvulsant action is unknown, but in animal test systems designed to detect anticonvulsant activity, gabapentin prevents seizures as do other marketed anticonvulsants. Gabapentin exhibits anti-seizure activity in mice and rats in both the maximal electroshock and pentylenetetrazole seizure models and other preclinical models (e.g., strains with genetic epilepsy, etc.). The relevance of these models to human epilepsy is not known.

Gabapentin is structurally related to the neurotransmitter GABA (gamma-aminobutyric acid) but it does not interact with GABA receptors, it is not converted metabolically into GABA or a GABA agonist, and it is not an inhibitor of GABA uptake or degradation. Gabapentin was tested in radioligand binding assays at concentrations up to 100μM and did not exhibit affinity for a number of other common receptor sites, including benzodiazepine, glutamate, N-methyl-D-aspartate (NMDA), quisqualate, kainate, strychnine-insensitive or strychnine-sensitive glycine, alpha 1, alpha 2, or beta adrenergic, adenosine A1 or A2, cholinergic muscarinic or nicotinic, dopamine D1 or D2, histamine H1, serotonin S1 or S2, opiate mu, delta or kappa, voltage-sensitive calcium channels sites labeled with nitrendipine or diltiazem, or at voltage-sensitive sodium channel sites with batrachotoxinin A 20-alpha-benzoate.

Several test systems ordinarily used to assess activity at the NMDA receptor have been examined. Results are contradictory. Accordingly, no general statement about the effects, if any, of gabapentin at the NMDA receptor can be made.

In vitro studies with radiolabeled gabapentin have revealed a gabapentin binding site in areas of rat brain including neocortex and hippocampus. The identity and function of this binding site remain to be elucidated.

Pharmacokinetics and Drug Metabolism:

All pharmacological actions following gabapentin administration are due to the activity of the parent compound; gabapentin is <u>not</u> appreciably metabolized in humans.

Oral bioavailability

Gabapentin bioavailability is not dose proportional; i.e., as dose is increased, bioavailability decreases. A 400 mg dose, for example is about 25% less bioavailable than a 100 mg dose. Over the recommended dose range of 300 to 600 mg T.I.D., however, the differences in bioavailability are not large, and bioavailability is about 60 percent. Food has no effect on the rate and extent of absorption of gabapentin.

Distribution

Gabapentin circulates largely unbound (< 3%) to plasma protein. The apparent volume of distribution of gabapentin after 150 mg intravenous administration is 58 ±6 L (Mean ±SD). In patients with epilepsy, steady-state predose (Cmin) concentrations of gabapentin in cerebrospinal fluid were approximately 20% of the corresponding plasma concentrations.

Elimination

Gabapentin is eliminated from the systemic circulation by renal excretion as unchanged drug. Gabapentin is not appreciably metabolized in humans.

Gabapentin elimination half-life is 5 to 7 hours and is unaltered by dose or following multiple dosing. Gabapentin elimination rate constant, plasma clearance, and renal clearance are directly proportional to creatinine clearance (see Special Populations: patients with renal insufficiency, below). In elderly patients, and in patients with impaired renal function, gabapentin plasma clearance is reduced. Gabapentin can be removed from plasma by hemodialysis.

Dosage adjustment in patients with compromised renal function or undergoing hemodialysis is recommended (see DOSAGE AND ADMINISTRATION, Table 2).

Special Populations

Patients with renal insufficiency: Subjects (N=60) with renal insufficiency (mean creatinine clearance ranging from 13-114 ml/min) were administered single 400 mg oral doses of gabapentin. The mean gabapentin half-life ranged from about 6.5 hours (patients with creatinine clearance > 60 ml/min) to 52 hours (creatinine clearance <30 ml/min) and gabapentin renal clearance from about 90 ml/min (> 60 ml/min group) to about 10 ml/min (<30 ml/min). Mean plasma clearance (CL/F) decreased from approximately 190 ml/min to 20 ml/min.

Dosage adjustment in patients with compromised renal function is necessary (see DOSAGE AND ADMINISTRATION).

Hemodialysis: In a study in anuric subjects (n=11), the apparent elimination half-life of gabapentin on non-dialysis days was about 132 hours; dialysis three times a week(4 hours duration) lowered the apparent half-life of gabapentin by about 60%, from 132 hours to 51 hours. Hemodialysis thus has a significant effect on gabapentin elimination in anuric subjects.

Dosage adjustment in patients undergoing hemodialysis is necessary (see DOSAGE AND ADMINISTRATION).

Hepatic disease: Because gabapentin is not metabolized, no study was performed in patients with hepatic impairment.

Age: The effect of age was studied in subjects 20-80 years of age. Apparent oral clearance (CL/F) of gabapentin decreased as age increased, from about 225 ml/min in those under 30 years of age to about 125 ml/min in those over 70 years of age. Renal clearance (CLr) and CLr adjusted for body surface area also declined with age; however, the decline in renal clearance of gabapentin with age can largely be explained by the decline in renal function. Reduction of gabapentin dose may be required in patients who have age related compromised renal function. (See Precautions, Geriatric Use, and Dosage and Administration.)

Pediatric: No pharmacokinetic data are available in children below the age of 18 years.

Gender: Although no formal study has been conducted to compare the pharmacokinetics of gabapentin in men and women, it appears that the pharmacokinetic parameters for males and females are similar and there are no significant gender differences.

Race: Pharmacokinetic differences due to race have not been studied. Because gabapentin is primarily renally excreted and there are no important racial differences in creatinine clearance, pharmacokinetic differences due to race are not expected.

Clinical Studies:

The effectiveness of Neurontin® as adjunctive therapy (added to other antiepileptic drugs) was established in three multicenter placebo-controlled, double-blind, parallel-group clinical trials in 705 adults with refractory partial seizures. The patients enrolled had a history of at least 4 partial seizures per month in spite of receiving one or more antiepileptic drugs at therapeutic levels and were observed on their established antiepileptic drug regimen during a 12-week baseline period. In patients continuing to have at least 2 (or 4 in some studies) seizures per month, Neurontin® or placebo was then added on to the existing therapy during a 12-week treatment period. Effectiveness was assessed primarily on the basis of the percent of patients with a 50% or greater reduction in seizure frequency from baseline to treatment (the "responder rate") and a derived measure called response ratio, a measure of change defined as $(T - B)/(T + B)$, where B is the patient's baseline seizure frequency and T is the patient's seizure frequency during treatment. Response ratio is distributed within the range -1 to +1. A zero value indicates no change while complete elimination of seizures would give a value of -1; increased seizure rates would give positive values. A response ratio of -0.33 corresponds to a 50% reduction in seizure frequency. The results given below are for all partial seizures in the intent-to-treat (all patients who received any doses of treatment) population in each study, unless otherwise indicated.

One study compared Neurontin® 1200 mg/day T.I.D. with placebo. Responder rate was 23% (14/61) in the Neurontin® group and 9% (6/66) in the placebo group; the difference between groups was statistically significant. Response ratio was also better in the Neurontin® group (-0.199) than in the placebo group (-0.044), a difference that also achieved statistical significance.

A second study compared primarily 1200 mg/day T.I.D. Neurontin® (N = 101) with placebo (N = 98). Additional smaller Neurontin® dosage groups (600 mg/day, N = 53; 1800 mg/day, N = 54) were also studied for information regarding dose response. Responder rate was higher in the Neurontin® 1200 mg/day group (16%) than in the placebo group (8%), but the difference was not statistically significant. The responder rate at 600 mg (17%) was also not significantly higher than in the placebo, but the responder rate in the 1800 mg group (26%) was statistically significantly superior to the placebo rate. Response ratio was better in the Neurontin® 1200 mg/day group (-0.103) than in the placebo group (-0.022), but this difference was also not statistically significant (p =0.224). A better response was seen in the Neurontin® 600 mg/day group (-0.105) and 1800 mg/day group (-0.222) than in the 1200 mg/day group, with the 1800 mg/day group achieving statistical significance compared to the placebo group.

A third study compared Neurontin® 900 mg/day T.I.D. (N = 111) and placebo (N = 109). An additional Neurontin® 1200 mg/day dosage group (N = 52) provided dose-response data. A statistically significant

difference in responder rate was seen in the Neurontin® 900 mg/day group (22%) compared to that in the placebo group (10%). Response ratio was also statistically significantly superior in the Neurontin® 900 mg/day group (-0.119) compared to that in the placebo group (-0.027), as was response ratio in the 1200 mg/day Neurontin® (-0.184) compared to placebo.

Analyses were also performed in each study to examine the effect of Neurontin on preventing secondarily generalized tonic-clonic seizures. Patients who experienced a secondarily generalized tonic clonic seizure in either the baseline or in the treatment period in all three placebo controlled studies were included in these analyses. There were several response ratio comparisons that showed a statistically significant advantage for Neurontin compared to placebo and favorable trends for almost all comparisons.

Analysis of responder rate using combined data from all three studies and all doses (N = 162, Neurontin®; N = 89, placebo) also showed a significant advantage for Neurontin® over placebo in reducing the frequency of secondarily generalized tonic-clonic seizures.

In two of the three controlled studies, more that one dose of Neurontin was used. Within each study the results did not show a consistently increased response to dose. (see Figure 1).

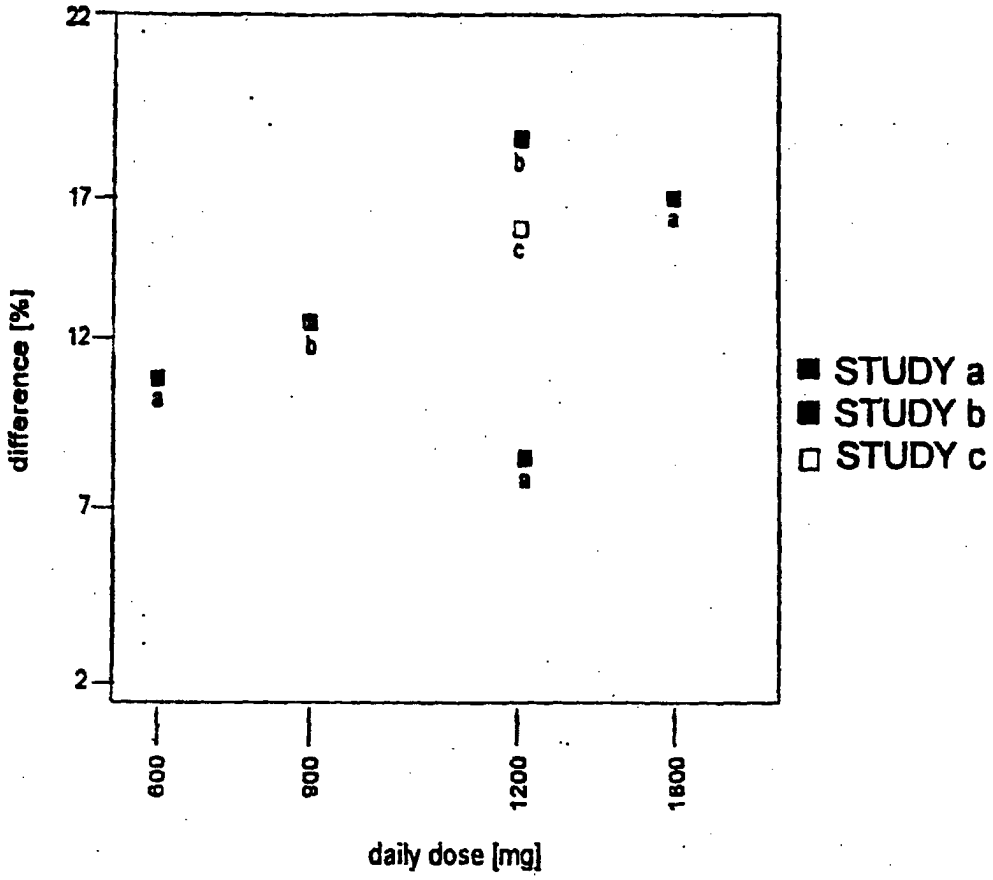


FIGURE 1. Responder Rate in Patients Receiving Neurontin® Expressed as a Difference from Placebo by Dose and Study

In the figure, treatment effect magnitude, measured on the Y axis in terms of the difference in the proportion of gabapentin and placebo assigned patients attaining a 50% or greater reduction in seizure frequency from baseline, is plotted against the daily dose of gabapentin administered (X axis).

Although no formal analysis by gender has been performed, estimates of response (Response Ratio) derived from clinical trials (398 men, 307 women) indicate no important gender differences exist. There was no consistent pattern indicating that age had any effect on the response to Neurontin®. There were insufficient numbers of patients of races other than Caucasian to permit a comparison of efficacy among racial groups.

INDICATIONS AND USAGE

Neurontin® (gabapentin) is indicated as adjunctive therapy in the treatment of partial seizures with and without secondary generalization in adults with epilepsy.

CONTRAINDICATIONS

Neurontin® is contraindicated in patients who have demonstrated hypersensitivity to the drug or its ingredients.

WARNINGS

Withdrawal precipitated seizure, Status Epilepticus:

Antiepileptic drugs should not be abruptly discontinued because of the possibility of increasing seizure frequency.

In the placebo-controlled studies, the incidence of status epilepticus in patients receiving Neurontin® was 0.6% (5 of 543) versus 0.5% in patients receiving placebo (2 of 378). Among the 2074 patients treated with Neurontin® across all studies (controlled and uncontrolled) 31 (1.5%) had status epilepticus. Of these, 14 patients had no prior history of status epilepticus either before treatment or while on other medications. Because adequate historical data are not available, it is impossible to say whether or not treatment with Neurontin is associated with a higher or lower rate of status epilepticus than would be expected to occur in a similar population not treated with Neurontin.

Tumorigenic potential:

In standard preclinical in-vivo lifetime carcinogenicity studies, an unexpectedly high incidence of pancreatic acinar adenocarcinomas was identified in male, but not female, rats. (See Carcinogenesis, mutagenesis, impairment of fertility). The clinical significance of this finding is unknown. Clinical experience during gabapentin's pre-marketing development provides no direct means to assess its potential for inducing tumors in humans.

In clinical studies comprising 2085 patient-years of exposure, new tumors were reported in 10 patients (2 breast, 3 brain, 2 lung, 1 adrenal, 1 non-Hodgkin's lymphoma, 1 endometrial carcinoma *in situ*) and pre-existing tumors worsened in 11 patients (9 brain, 1 breast, 1 prostate) during or up to 2 years following discontinuation of Neurontin®. Without

knowledge of the background incidence and recurrence in a similar population not treated with Neurontin®, it is impossible to know whether the incidence seen in this cohort is or is not affected by treatment.

Sudden and unexplained deaths:

During the course of Neurontin®'s premarketing development, 8 sudden and unexpected deaths were recorded among a cohort of 2204 patients (2103 patient-years of exposure).

Some of these could represent seizure-related deaths in which the seizure was not observed, e.g., at night. This represents an incidence of 0.0038 deaths per patient-year. Although this rate exceeds that expected in a healthy population matched for age and sex, it is within the range of estimates for the incidence of sudden unexplained deaths in patients with epilepsy not receiving Neurontin® (ranging from 0.0005 for the general population of epileptics, to 0.003 for a clinical trial population similar to that in the Neurontin® program to 0.005 for patients with refractory epilepsy). Consequently, whether these figures are reassuring or raise further concern depends on comparability of the populations reported upon to the Neurontin® cohort and the accuracy of the estimates provided.

PRECAUTIONS

Information for Patients:

Patients should be instructed to take Neurontin® only as prescribed.

Patients should be advised that Neurontin® may cause dizziness, somnolence and other symptoms and signs of CNS depression. Accordingly, they should be advised neither to drive a car nor to operate other complex machinery until they have gained sufficient experience on Neurontin® to gauge whether or not it affects their mental and/or motor performance adversely.

Laboratory Tests:

Clinical trials data do not indicate that routine monitoring of clinical laboratory parameters is necessary for the safe use of Neurontin®. The value of monitoring Neurontin® blood concentrations has not been established. Neurontin® may be used in combination with other antiepileptic drugs without concern for alteration of the blood concentrations of gabapentin or of other antiepileptic drugs.

Drug Interactions:

Gabapentin is not appreciably metabolized nor does it interfere with the metabolism of commonly co-administered anti-epileptic drugs.

The drug interaction data described in this section were obtained from and studies involving healthy adults and patients with epilepsy.

Phenytoin: In a single and multiple dose study of Neurontin® (400 mg T.I.D.) in epileptic patients (N=8) maintained on phenytoin monotherapy for at least 2 months, gabapentin had no effect on the steady-state trough plasma concentrations of phenytoin and phenytoin had no effect on gabapentin pharmacokinetics.

Carbamazepine: Steady-state trough plasma carbamazepine and carbamazepine 10, 11 epoxide concentrations were not affected by concomitant gabapentin (400 mg T.I.D.; N=12) administration. Likewise, gabapentin pharmacokinetics were unaltered by carbamazepine administration.

Valproic Acid: The mean steady state trough serum valproic acid concentrations prior to and during concomitant gabapentin administration (400 mg T.I.D.; N = 17) were not different and neither were gabapentin pharmacokinetic parameters affected by valproic acid.

Phenobarbital: Estimates of steady-state pharmacokinetic parameters for phenobarbital or gabapentin (300 mg T.I.D.; N=12) are identical whether the drugs are administered alone or together.

Cimetidine: In the presence of cimetidine at 300 mg Q.I.D. (N=12) the mean apparent oral clearance of gabapentin fell by 14% and creatinine clearance fell by 10%. Thus cimetidine appeared to alter the renal excretion of both gabapentin and creatinine, an endogenous marker of renal function. This small decrease in excretion of gabapentin by cimetidine is not expected to be of clinical importance. The effect of gabapentin on cimetidine was not evaluated.

Oral Contraceptive: Based on AUC and half-life, multiple-dose pharmacokinetic profiles of norethindrone and ethinyl estradiol following administration of tablets containing 2.5mg of norethindrone acetate and 50 mcg of ethinyl estradiol were similar with and without coadministration of gabapentin (400 mg T.I.D.; N=13). The Cmax of norethindrone was 13% higher when it was coadministered with gabapentin; this interaction is not expected to be of clinical importance.

Antacid (Maalox): Maalox reduced the bioavailability of gabapentin (N = 16) by about 20%. This decrease in bioavailability was about 5% when gabapentin was administered 2 hours after Maalox. It is recommended that gabapentin be taken at least 2 hours following Maalox administration.

Effect of Probenecid: Probenecid is a blocker of renal tubular secretion. Gabapentin pharmacokinetic parameters without and with probenecid were comparable. This indicates that gabapentin does not undergo renal tubular secretion by the pathway that is blocked by probenecid.

Drug/Laboratory Tests Interactions: Because false positive readings were reported with the Ames N-Multistix SG® dipstick test for urinary protein when gabapentin was added to other antiepileptic drugs, the more specific sulfosalicylic acid precipitation procedure is recommended to determine the presence of urine protein.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Gabapentin was given in the diet to mice at 200, 600, and 2000 mg/kg/day and to rats at 250, 1000, and 2000 mg/kg/day for 2 years. A statistically significant increase in the incidence of pancreatic acinar cell adenomas and carcinomas was found in male rats receiving the high dose; the no-effect dose for the occurrence of carcinomas was 1000 mg/kg/day. Peak plasma concentrations of gabapentin in rats receiving the high dose of 2000 mg/kg/day were 10 times higher than plasma concentrations in humans receiving 3600 mg per day and in rats receiving 1000 mg/kg/day peak plasma concentrations were 6.5 times higher than in humans receiving 3600 mg/day. The pancreatic acinar cell carcinomas did not affect survival, did not metastasize and were not locally invasive. Studies to attempt to define a mechanism by which this relatively rare tumor type is occurring are in progress. The relevance of this finding to carcinogenic risk in humans is unclear.

Gabapentin did not demonstrate mutagenic or genotoxic potential in three *in vitro* and two *in vivo* assays. It was negative in the Ames test and the *in vitro* HGPRT forward mutation assay in Chinese hamster lung cells; it did not produce significant increases in chromosomal abberations in the *in vitro* Chinese hamster lung cell assay; it was negative in the *in vivo* chromosomal aberration assay and in the *in vivo* micronucleus test in Chinese hamster bone marrow.

No adverse effects on fertility or reproduction were observed in rats at doses up to 2000 mg/kg (approximately 5 times the maximum recommended human dose on a mg/m^2 basis).

Pregnancy: Pregnancy category C.

Gabapentin has been shown to be fetotoxic in rodents, causing delayed ossification of several bones in the skull, vertebrae, forelimbs and hindlimbs. These effects occurred when pregnant mice received oral doses of 1000 or 3000 mg/kg/day during the period of organogenesis, or approximately 1 to 4 times the maximum dose of 3600 mg/day given to epileptic patients on a mg/m^2 basis. The no effect level was 500 mg/kg/day or approximately 1/2 of the human dose on a mg/m2 basis.

When rats were dosed prior to and during mating, and throughout gestation, pups from all dose groups (500, 1000 and 2000 mg/kg/day) were affected. These doses are equivalent to less than approximately 1 to 5 times the maximum human dose on a mg/m^2 basis. There was an increased incidence of hydroureter and/or hydronephrosis in rats in a study of fertility and general reproductive performance at 2000 mg/kg/day with no effect at 1000 mg/kg/day, in a teratology study at 1500 mg/kg/day with no effect at 300 mg/kg/day, and in a perinatal and postnatal study at all doses studied (500, 1000 and 2000 mg/kg/day). The doses at which the effects occurred are approximately 1 to 5 times the maximum human dose of 3600 mg/day on a mg/m^2 basis; the no effect doses were approximately 3 times (Fertility and General Reproductive

Performance study) and approximately equal to (Teratogenicity study) the maximum human dose on a mg/m^2 basis. Other than hydroureter and hydronephrosis, the etiologies of which are unclear, the incidence of malformations was not increased compared to controls in offspring of mice, rats, or rabbits given doses up to 50 times (mice), 30 times (rats), and 25 times (rabbits) the human daily dose on a mg/kg basis, or 4 times (mice), 5 times (rat), or 8 times (rabbit) the human daily dose on a mg/m^2 basis.

In a teratology study in rabbits, an increased incidence of postimplantation fetal loss occurred in dams exposed to 60, 300 and 1500 mg/kg/day, or less than approximately 1/4 to 8 times the maximum human dose on a mg/m^2 basis. There are no adequate and well controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Use in Nursing Mothers: It is not known if gabapentin is excreted in human milk and the effect on the nursing infant is unknown. However, because many drugs are excreted in human milk, Neurontin should be used in women who are nursing only if the benefits clearly outweigh the risks.

Pediatric Use: Safety and effectiveness in children below the age of 12 years have not been established.

Geriatric Use: No systematic studies in geriatric patients have been conducted. Adverse clinical events reported among 59 Neurontin exposed patients over age 65 did not differ in kind from those reported for younger individuals. The small number of older individuals evaluated, however, limits the strength of any conclusions reached about the influence, if any, of age on the kind and incidence of adverse event or laboratory abnormality associated with the use of Neurontin.

Because Neurontin® is eliminated almost exclusively by renal excretion, the dose of Neurontin® should be adjusted as noted in Dosage and Administration (Table 2) for elderly patients with compromised renal function. Creatinine clearance is difficult to measure in outpatients and serum creatinine may be reduced in the elderly because of decreased muscle mass. Creatinine clearance (C_{Cr}) can be reasonably well estimated using the equation of Cockcroft and Gault:

for females $C_{cr}=(0.85)(140-age)(wt)/(72)(Scr)$

for males $C_{cr}=(140-age)(wt)/(72)(Scr)$

where age is in years, wt is in kilograms and S_{cr} is serum creatinine in mg/dl.

ADVERSE REACTIONS

The most commonly observed adverse events associated with the use of Neurontin® in combination with other antiepileptic drugs, not seen at an equivalent frequency among placebo-treated patients, were somnolence, dizziness, ataxia, fatigue, and nystagmus.

Approximately 7% of the 2074 individuals who received Neurontin® in premarketing clinical trials discontinued treatment because of an adverse event. The adverse events most commonly associated with withdrawal were somnolence (1.2%), ataxia (0.8%), fatigue (0.6%), nausea and/or vomiting (0.6%), and dizziness (0.6%).

Incidence in Controlled Clinical Trials: Table 1 lists treatment-emergent signs and symptoms that occurred in at least 1% of Neurontin®-treated patients with epilepsy participating in placebo-controlled trials and were numerically more common in the Neurontin® group. In these studies, either Neurontin® or placebo was added to the patient's current antiepileptic drug therapy. Adverse events were usually mild to moderate in intensity.

The prescriber should be aware that these figures, obtained when Neurontin® was added to concurrent antiepileptic drug therapy, cannot be used to predict the frequency of adverse events in the course of usual medical practice where patient characteristics and other factors may differ from those prevailing during clinical studies. Similarly, the cited

frequencies cannot be directly compared with figures obtained from other clinical investigations involving different treatments, uses, or investigators. An inspection of these frequencies, however, does provide the prescribing physician with one basis to estimate the relative contribution of drug and non-drug factors to the adverse event incidences in the population studied.

TABLE 1. Treatment-Emergent Adverse Event Incidence in Controlled Add-On Trials (Events in at least 1% of Neurontin patients and numerically more frequent than in the placebo group)

Body System/ Adverse Event	Neurontin[a] N = 543 %	Placebo[a] N = 378 %
Body As A Whole		
Fatigue	11.0	5.0
Weight Increase	2.9	1.6
Back Pain	1.8	0.5
Peripheral Edema	1.7	0.5
Cardiovascular		
Vasodilatation	1.1	0.3
Digestive System		
Dyspepsia	2.2	0.5
Mouth or Throat Dry	1.7	0.5
Constipation	1.5	0.8
Dental Abnormalities	1.5	0.3
Increased Appetite	1.1	0.8
Hematologic and Lymphatic Systems		
Leukopenia	1.1	0.5
Musculoskeletal System		
Myalgia	2.0	1.9
Fracture	1.1	0.8
Nervous System		
Somnolence	19.3	8.7
Dizziness	17.1	6.9
Ataxia	12.5	5.6
Nystagmus	8.3	4.0
Tremor	6.8	3.2
Nervousness	2.4	1.9
Dysarthria	2.4	0.5
Amnesia	2.2	0.0
Depression	1.8	1.1
Thinking Abnormal	1.7	1.3

[a] Plus background antiepileptic drug therapy
[b] Amblyopia was often described as blurred vision

TABLE 1. Treatment-Emergent Adverse Event Incidence in Controlled Add-On Trials (Events in at least 1% of Neurontin patients and numerically more frequent than in the placebo group)

Body System/ Adverse Event	Neurontine[a] N = 543 %	Placebo[a] N = 378 %
Nervous System (cont)		
Twitching	1.3	0.5
Coordination Abnormal	1.1	0.3
Respiratory System		
Rhinitis	4.1	3.7
Pharyngitis	2.8	1.6
Coughing	1.8	1.3
Skin and Appendages		
Abrasion	1.3	0.0
Pruritus	1.3	0.5
Urogenital System		
Impotence	1.5	1.1
Special Senses		
Diplopia	5.9	1.9
Amblyopia[b]	4.2	1.1
Laboratory Deviations		
WBC Decreased	1.1	0.5

[a] Plus background antiepileptic drug therapy
[b] Amblyopia was often described as blurred vision

Other events in more than 1% of patients but equally or more frequent in the placebo group included: headache, viral infection, fever, nausea and /or vomiting, abdominal pain, diarrhea, convulsions, confusion, insomnia, emotional lability, rash, acne.

Among the treatment-emergent adverse events occurring at an incidence of at least 10% of Neurontin®-treated patients, somnolence and ataxia appeared to exhibit a positive dose-response relationship.

The overall incidence of adverse events and the types of adverse events seen were similar among men and women treated with Neurontin®. The incidence of adverse events increased slightly with age in patients treated with either Neurontin® or placebo. Because only 3% of patients (28/921) in placebo-controlled studies were identified as nonwhite (black or other), there are insufficient data to support a statement regarding the distribution of adverse events by race.

Other Adverse Events Observed During All Clinical Trials

Other Adverse Events: Neurontin® has been administered to 2074 individuals during all clinical trials, only some of which were placebo-controlled. During these trials, all adverse events were recorded by the clinical investigators using terminology of their own choosing. To provide a meaningful estimate of the proportion of individuals having adverse events, similar types of events were grouped into a smaller number of

standardized categories using modified COSTART dictionary terminology. These categories are used in the listing below. The frequencies presented represent the proportion of the 2074 individuals exposed to Neurontin® who experienced an event of the type cited on at least one occasion while receiving Neurontin®. All reported events are included except those already listed in the previous table, those too general to be informative, and those not reasonably associated with the use of the drug.

Events are further classified within body system categories and enumerated in order of decreasing frequency using the following definitions: frequent adverse events are defined as those occurring in at least 1/100 patients; infrequent adverse events are those occurring in 1/100 to 1/1000 patients; rare events are those occurring in fewer than 1/1000 patients.

Body As A Whole: *Frequent:* asthenia, malaise, face edema; *Infrequent:* allergy, generalized edema, weight decrease, chill; *Rare:* strange feelings, lassitude, alcohol intolerance, hangover effect.

Cardiovascular System: *Frequent:* hypertension; *Infrequent:* hypotension, angina pectoris,peripheral vascular disorder, palpitation, tachycardia, hypertension, migraine, murmur; *Rare:* atrial fibrillation, heart failure, thrombophlebitis, deep thrombophlebitis, myocardial infarction, cerebrovascular accident, pulmonary thrombosis, ventricular extrasystoles, bradycardia, premature atrial contraction, pericardial rub,

heart block, pulmonary embolus, hyperlipidemia, hypercholesterolemia, pericardial effusion, pericarditis.

Digestive System: *Frequent*: anorexia, flatulence, gingivitis; *Infrequent*: glossitis, gum hemorrhage, thirst, stomatitis, increased salivation, gastroenteritis, hemorrhoids, bloody stools, fecal incontinence, hepatomegaly; *Rare*: dysphagia, eructation, pancreatitis, peptic ulcer, colitis, blisters in mouth, tooth discolor, perleche, salivary gland enlarged, lip hemorrhage, esophagitis, hiatal hernia, hematemesis, proctitis, irritable bowel syndrome, rectal hemorrhage, esophageal spasm.

Endocrine System: *Rare*: hyperthyroid, hypothyroid, goiter, hypoestrogen, ovarian failure, epididymitis, swollen testicle, cushingoid appearance.

Hematologic and Lymphatic System: *Frequent:* purpura most often described as bruises resulting from physical trauma; *Infrequent:* anemia, thrombocytopenia, lymphadenopathy; *Rare*: WBC count increased, lymphocytosis, non-Hodgkin's lymphoma, bleeding time increased.

Musculoskeletal System: *Frequent*: arthralgia; *Infrequent*: tendinitis, arthritis, joint stiffness, joint swelling, positive Romberg test; *Rare*: costochondritis, osteoporosis bursitis, contracture.

Nervous System: *Frequent*: vertigo, hyperkinesia, paresthesia, decreased or absent reflexes, increased reflexes,anxiety, hostility; *Infrequent*: CNS tumors, syncope, dreaming abnormal, aphasia, hypesthesia,

intracranial hemorrhage, hypotonia, dysesthesia, paresis, dystonia, hemiplegia, facial paralysis, stupor, cerebellar dysfunction, positive Babinski sign, decreased position sense, subdural hematoma, apathy, hallucination, decrease or loss of libido, agitation, paranoia, depersonalization, euphoria, feeling high, doped-up sensation, suicidal, psychosis; *Rare*: choreoathetosis,orofacial dyskinesia, encephalopathy, nerve palsy, personality disorder, increased libido, subdued temperament, apraxia, fine motor control disorder, meningismus, local myoclonus, hyperesthesia, hypokinesia, mania, neurosis, hysteria, antisocial reaction, suicide gesture.

Respiratory System: *Frequent*: pneumonia; *Infrequent*: epistaxis, dyspnea, apnea; *Rare:* mucositis, aspiration pneumonia, hyperventilation, hiccup, laryngitis;nasal obstruction, snoring, bronchospasm, hypoventilation, lung edema.

Dermatological: *Infrequent:* alopecia, eczema, dry skin, increased sweating, urticaria, hirsutism, seborrhea, cyst, herpes simplex; *Rare*: herpes zoster, skin discolor, skin papules, photosensitive reaction, leg ulcer, scalp seborrhea, psoriasis, desquamation, maceration, skin nodules, subcutaneous nodule, melanosis, skin necrosis, local swelling.

Urogenital System: *Infrequent*: hematuria, dysuria, urination frequency, cystitis, urinary retention, urinary incontinence, vaginal hemorrhage, amenorrhea, dysmenorrhea, menorrhagia, breast cancer, unable to climax, ejaculation abnormal; *Rare*: kidney pain, leukorrhea, pruritus genital,

renal stone, acute renal failure, anuria, glycosuria, nephrosis, nocturia, pyuria, urination urgency, vaginal pain, breast pain, testicle pain.

Special Senses: *Frequent:* abnormal vision; *Infrequent*: cataract, conjunctivitis, eyes dry, eye pain, visual field defect, photophobia, bilateral or unilateral ptosis, eye hemorrhage, hordeolum, hearing loss, earache, tinnitus, inner ear infection, otitis, taste loss, unusual taste, eye twitching, ear fullness; *Rare*: eye itching, abnormal accommodation, perforated ear drum, sensitivity to noise, eye focusing problem, watery eyes, retinopathy, glaucoma, iritis, corneal disorders, lacrimal dysfunction, degenerative eye changes, blindness, retinal degeneration, miosis, chorioretinitis, strabismus, eustachian tube dysfunction, labyrinthitis, otitis externa, odd smell.

DRUG ABUSE AND DEPENDENCE

The abuse and dependence potential of Neurontin® have not been evaluated in human studies.

OVERDOSAGE

A lethal dose of gabapentin was not identified in mice and rats receiving single oral doses as high as 8000 mg/kg. Signs of acute toxicity in animals included ataxia, labored breathing, ptosis, sedation, hypoactivity, or excitation.

Acute oral overdoses of Neurontin® up to 49 grams have been reported. In these cases, double vision, slurred speech, drowsiness, lethargy and diarrhea were observed. All patients recovered with supportive care.

Gabapentin can be removed by hemodialysis. Although hemodialysis has not been performed in the few overdose cases reported, it may be indicated by the patient's clinical state or in patients with significant renal impairment.

DOSAGE AND ADMINISTRATION

Neurontin® is recommended for add-on therapy in patients over 12 years of age. Evidence bearing on its safety and effectiveness in children is not available.

Neurontin is given orally with or without food.

The effective dose of Neurontin is 900 to 1800 mg/day and given in divided doses (three times a day) using 300- or 400-mg capsules. Titration to an effective dose can take place rapidly, over a few days, giving 300 mg on Day 1, 300 mg twice a day on Day 2, and 300 mg three times a day on Day 3. To minimize potential side effects, especially somnolence, dizziness, fatigue, and ataxia, the first dose on Day 1 may be administered at bedtime. If necessary, the dose may be increased using 300- or 400-mg capsules three times a day up to 1800 mg/day. Dosages up to 2400 mg/day have been well-tolerated in long-term clinical studies.

Doses of 3600 mg/day have also been administered to a small number of patients for a relatively short duration, and have been well tolerated. The maximum time between doses in the T.I.D. schedule should not exceed 12 hours.

It is not necessary to monitor gabapentin plasma concentrations to optimize Neurontin therapy. Further, because there are no significant pharmacokinetic interactions among Neurontin and other commonly used anti-epileptic drugs, the addition of Neurontin does not alter the plasma levels of these drugs appreciably.

If Neurontin is discontinued and/or an alternate anticonvulsant medication is added to the therapy, this should be done gradually over a minimum of 1 week.

Dosage adjustment in patients with compromised renal function or undergoing hemodialysis is recommended as follows:

TABLE 2. Neurontin® Dosage Based on Renal Function

Renal Function Creatinine Clearance (mL/min)	Total Daily Dose (mg/day)	Dose Regimen (mg)
>60	1200	400 TID
30 - 60	600	300 BID
15 - 30	300	300 QD
<15	150	300 QOD[a]
Hemodialysis	-	200-300[b]

[a] Every other day

[b] Loading dose of 300 to 400 mg in patients who have never received Neurontin®, then 200 to 300 mg Neurontin® following each 4 hours of hemodialysis

HOW SUPPLIED

Neurontin® (gabapentin capsules) are supplied as follows:

100-mg capsules:

White hard gelatin capsules printed with "PD" on one side and "Neurontin®/100 mg" on the other; available in:

Bottles of 100: N 0071-0803-24

Unit dose 50's: N 0071-0803-40

300-mg capsules;

Yellow hard gelatin capsules printed with "PD" on one side and "Neurontin®/300 mg" on the other; available in:

Bottles of 100: N 0071-0805-24

Unit dose 50's: N 0071-0805-40

400-mg capsules;

Orange hard gelatin capsules printed with "PD" on one side and "Neurontin® /400 mg" on the other; available in:

Bottles of 100: N 0071-0806-24

Unit dose 50's: N 0071-0806-40

Store at controlled room temperature 15 - 30°C (59-86°F).

Caution: Federal law prohibits dispensing without prescription.

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